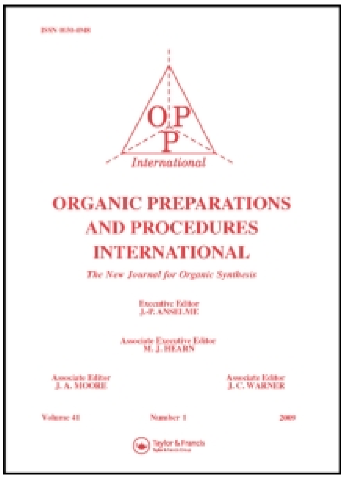

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AN EFFICIENT SYNTHESIS OF α,β-UNSATURATED CARBOXYLIC ACIDS AND NITRILES

Chang Kiu Lee[a]; Jeung Yeop Shim[a]
[a] Department of Chemistry, Kangweon National University, Chuncheon, KOREA

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305 (1970).

2. W. J. Rzeszotarski, W. C. Eckelman, B. E. Francis, D. A. Simms, R. E. Gibson, E. M. Jagoda, M. P. Grissom, R. R. Eng, J. J. Conklin and R. C. Reba, J. Med. Chem., 27, 156 (1984); W. J. Rzeszotarski, W. C. Eckelman, R. E. Gibson, D. A. Simms and R. C. Reba, J. Labelled Comp. Radiopharm., 18, 94 (1981).

3. W. C. Eckelman, In "Applications of Nuclear and Radiochemistry", R. Lambrecht, N. Marcos. Eds., Pergamon Press, Elmsford, NY, p. 287-298 (1982).

4. O. Wallach, Ann., 234, 242 (1888); N. I. Foster, H. D. Burns, N. D. Heindel, J. Radioanal. Chem., 65, 95 (1981).

5. G. W. Kabalka, K. A. R. Sastry and K. Muralidhar, J. Labelled Compd., Radiopharm., 19, 795 (1982).

6. 4-Iodobenzophenone was prepared by Friedel-Craft reaction of iodobenzene, benzoyl chloride in presence of $AlCl_3$. See: P. H. Gore, S. Thorburn and D. J. Weyell, J. Chem. Soc. Perkin I, 2940 (1973).

7. K. Fuji, N. Shigetoshi and E. Fujita, Synthesis, 276 (1975).

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AN EFFICIENT SYNTHESIS OF α,β-UNSATURATED CARBOXYLIC ACIDS AND NITRILES

Submitted by (03/20/89) Chang Kiu Lee* and Jeung Yeop Shim

Department of Chemistry
Kangweon National University
Chuncheon 200-701, KOREA

The preparation of α,β-unsaturated carboxylic acids and nitriles is of importance because of their usefulness in organic synthesis. Condensation of aldehydes with malonic acid or cyanoacetic acid at elevated temperature in the presence of nitrogen bases (Knoevenagel reaction) is commonly employed.[1,2] With aromatic aldehydes, the reaction gives the desired products although the yields vary depending upon the reaction conditions. However, the method does not appear to be suitable with aliphatic aldehydes, especially those of low bp because of poor yield and formation of side-products such as β,γ-unsaturated carboxylic acids. In addition, the long reaction time also seems deleterious.[3-5] Our attempts to reproduce the reported yield of crotonic acid from the reaction of acetaldehyde with malonic acid were not successful.[6] The preparation of α,β-unsaturated nitriles appears to be quite troublesome because of incomplete decarboxylation. Even with aromatic aldehydes the yields of cinnamonitriles are generally low.[7]

We now report an efficient method of the preparation of α,β-unsaturated carboxylic acids and nitriles in molar scale from aliphatic aldehydes and malonic acid and cyanoacetic acid, respectively.The key feature of this procedure is the use of a stainless steel bomb reactor. Pyridine containing a few drops of piperidine was used as solvent and catalyst. The reactor was connected to a water aspirator for about 10 min and sealed prior to heating at 190° for 2 hrs. The

$$\underset{1}{\text{R-CH=O}} \quad + \quad \underset{2}{\text{XCH}_2\text{COOH}} \quad \longrightarrow \quad \underset{3}{\text{R-CH=CH-X}}$$

pressure rose to 1000 psi during the course of the reaction. The yields and bp of the products are listed in the Table. This method is suitable with straight-chain aliphatic aldehydes. The low yields with acetadehyde and propionaldehyde seem to be due to the low boiling point of these compounds; rapid vaporization may prevent contact with the acid. Steric hindrance seems to be an important factor, thus accounting for the low yield of the product from isobutyraldehyde. Indeed, pivalaldehyde (trimethylacetaldehyde) and ketones (e. g., acetone) failed to react under similar conditions.

In contrast to the fact that only α,β-unsaturated carboxylic acids resulted from the reaction with malonic acid, β,γ-unsaturated nitriles were formed in addition to α,β-unsaturated nitriles with cyanoacetic acid. The ratio of β,γ- to α,β-unsaturated nitriles was *ca*. 1:4. They were not separable by fractional distilation. Regardless of the position of the double bond, the configuration of the unsaturated nitriles prepared by the present method was all *trans*, which was confirmed by the coupling constants values of their NMR spectra. Although mixtures of isomeric nitriles were obtained, the method seems to be useful because the yields are much higher (60-70%) than those previously reported for the preparation of pentenonitrile (25%) and hexenonitrile (28%).

EXPERIMENTAL SECTION

Materials. Aldehydes *1a-e*, malonic acid and cyanoacetic acid were purchased from the Aldrich Chemical Co. Commercial pyridine and piperidine were dried over KOH prior to distillation. The stainless steel bomb reactor (Parr Model 4761) has inner volume of 300 mL and internal diameter is 2.5 inches.

General Procedure.- In a stainless steel bomb reactor, cooled in an ice-acetone bath, were placed 1 mole of aldehyde and 1.5 mole of malonic acid. Pyridine (70 mL) and piperidine (2-3 drops) were added to the mixture. The reactor was connected to and evacuated with a water aspirator for a few min. and sealed; it was then placed in an oil bath at 190° for 2 hrs. After cooling to room temperature, the bomb was opened and the mixture was poured on finely crushed ice (150 g) and stirred until the ice melted. The aqueous solution was brought to pH 5 by adding conc. HCl and extracted with ether (3 x 80 mL). The organic extract was dried over Na_2SO_4 and distilled using a fractionation column (2.5 x 30 cm) under reduced pressure. The product was identified by comparison of its IR and NMR spectra with those of the literature and the purity was examined by gas chromatography. The nitriles were prepared by similar method using cyanoacetic acid.

TABLE. Yields and bps of α,β-Unsaturated Acids and Nitriles

Compd	R	X	Yield (%)	bp [°C/(mm)]	lit. bp [°C/(mm)]
3a	CH_3	CO_2H	55	86-90 (20)	189(760)[8]
3b	CH_2CH_3	CO_2H	70	92-102 (20)	108(17)[8]
3c	$CH_2CH_2CH_3$	CO_2H	85	118-122 (15)	118(19)[8]
3d	$CH(CH_3)_2$	CO_2H	30	120-125 (15)	115-116(20)[8]
3e	$C(CH_3)_3$	CO_2H	0		
3f	CH_3	CN	60	40-42 (40)[a]	107.4(757)[9]
3g	CH_2CH_3	CN	60	50-55 (40)[a]	59-60(72)[10]
3h	$CH_2CH_2CH_3$	CN	70	50-52 (20)[a]	164-165(755)[11]
3i	$C(CH_3)_3$	CN	0		

a) Distilled as a mixture of α,β- and β,γ-unsaturated nitriles (4:1 by NMR).

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REFERENCES

1. H. Henecka and E. Ott in "Methoden der Organischen Chemie," E. Muller, Ed., Vol. 8, p. 450, Verlag, Stuttgart, West Germany, 1952.
2. G. Jones, Org. React., 15, 204 (1967) and references therein.
3. A. A. Goldberg and R. P. Linstead, J. Chem. Soc. (London), 2343 (1928).
4. S. E. Boxer and R. P. Linstead, ibid., 740 (1931).
5. R. P. Linstead, E. G. Noble and E. J. Boorman, ibid., 557 (1933).
6. S. Dutt, J. Indian Chem. Soc., 1, 297 (1925).
7. Reference 2, p. 378.
8. J. R. A. Pollock and R. Stevens, Ed., "Dictionary of Organic Compounds", Oxford University Press, NY, 1965: (a) Vol. 2, p. 754; (b) Vol. 4, p. 2634; (c) Vol. 3, p. 1614; (d) Vol 4, 2285.
9. G. Heim, Bull. Soc. Chim. Belg., 42, 461 (1933).
10. P. Bruylants and G. Jmoudsky, Bull. Sci. Acad. Roy. Belg., 17, 1161 (1931); Chem.

Abs., 26, 3232 (1932).

11. P. Bruylants, Bull. Soc. Chim. Belg., 41, 309 (1932).

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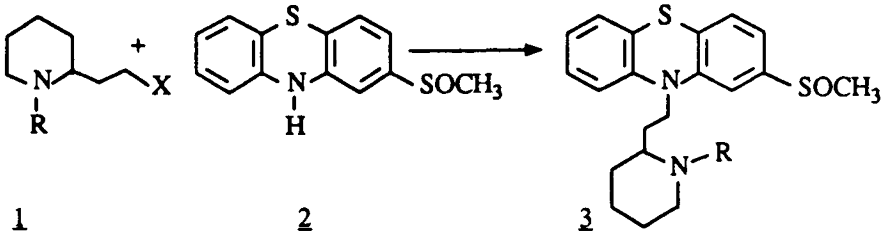
SYNTHESIS OF N-DESMETHYL MESORIDAZINE

Submitted by (02/07/89)

T. Mohammad †, E. M. Hawes* and K. K. Midha

College of Pharmacy, University of Saskatchewan
Saskatoon, Saskatchewan S7N 0W0, CANADA

10-[2-(2-Pipridinyl)ethyl]-2-methylsulfinyl-10H-phenothiazine (N-desmethyl mesoridazine, 3b), a metabolite of mesoridazine (3c) is a piperidine-type phenothiazine antipsychotic agent which was needed for studies of the metabolism and disposition of mesoridazine as an internal standard for its quantitation in the body fluids and for the preparation of hapten to conjugate with proteins. We found only one report[1] of the synthesis of 3b by direct condensation of 1b with 2 using sodium amide in refluxing toluene. However, under similar reaction conditions (sodium hydroxide in refluxing toluene), we either failed to obtain 3b or it was isolated in only very poor yield (~ 5%). The N-10 alkylation of 2 with 1b did not succeed most likely because the latter is known to undergo intramolecular cyclodehydrohalogenation under basic conditions to form conidine.[2]



1 2 3

a) R = CHO
b) R = H
c) R = CH_3

a) R = H, X = OH c) R = CHO, X = OH

b) R = H, X = Cl d) R = CHO, X = Cl

Although mesoridazine (3c) is available in large quantities, its N-demethylation is plagued by two problems:[3] (i) competing N-dealkylation at the 10-position of the phenothiazine ring, and (ii) lability of the sulfoxide group under the acidic conditions[4] employed for demethylation. The difficulties were overcome by the preparation of 1d from 1a followed by condensation of 1d with 2 (sodium hydroxide in refluxing toluene) to form 3a (not isolated);[5] alkaline hydrolysis of 3a in ethanol provided N-desmethyl mesoridazine (3b). The overall yield from 1a was 29%.